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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/285,531 | 04/02/1999 | YUTI CHERNAJOVSKY | KIR95-01A | 3818 |
| 7590 06/02/2004 | | | | |
| JOHN P. WHITE, ESQ. COOPER AND DUNHAM 1185 AVENUE OF THE AMERICAS NEW YORK, NY 10036 | | EXAMINER O HARA, EILEEN B | | |
| | | ART UNIT PAPER NUMBER 1646 | | |

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/285,531

Applicant(s)

CHERNAJOVSKY ET AL.

Examiner

Eileen O'Hara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,6,8,14-17 and 19-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 29-31 is/are allowed.
- 6) ☒ Claim(s) 1-3,6,8,15-17 and 19-27 is/are rejected.
- 7) ☒ Claim(s) 14,28 and 32-37 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 April 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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DETAILED ACTION

1. Claims 1-3, 6, 8, 14-17 and 19-37 are pending in the instant application. Claims 1, 14, 17, 28 and 30-32 have been amended as requested by Applicant in the Paper filed March 4, 2004.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

- 3.1 Claims 1-3, 6, 8, 15-17 and 19-27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wallach et al., U.S. Patent No. 5,478,925 (Wallach I), or Wallach et al., EP 0 526 905 (Wallach II), in view of Paul et al., U.S. Patent No. 5,736,387, for reasons of record in the previous Office Actions, Paper No. 28, Paper No. 26, Paper No. 20, Paper No. 18, and Paper No. 8, and below.

Claims 1-3, 6, 8, 15-17 and 19-27 also remain rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. PN 5,395,760, March 7, 1995, view of Paul et al., U.S. Patent No.

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5,736,387, for reasons of record in the previous Office Actions, Paper No. 28, Paper No. 26, Paper No. 20, Paper No. 18, and Paper No. 8, and below.

Claims drawn to the nucleic acid of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2 have been withdrawn from the rejections, because the references of record do not suggest the single claimed species with the particularity required to support a prima facie case of obviousness. *Compare In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The teachings of Wallach et al. (I and II) and Paul et al. were discussed in the previous office actions, and the teachings of Smith et al. and Paul et al. were also discussed in the previous office actions. Applicants traverse the rejection under Wallach et al. (I and II) and Paul et al. on pages 16-21 of the response, and the rejection under Smith et al. and Paul et al. on pages 22-23 of the response. Since the issues are the same for both rejections, they will be addressed together.

Applicants traverse the rejections and assert that the Examiner has failed to establish a *prima facie* case of obviousness, and incorporate their remarks in previous communications (page 16). Applicants maintain that the claimed molecule is unexpectedly superior to known TNF receptor-based molecules, by having a low molecular weight, an optimal linker length, and absence of an Ig Fc domain which has the potential cause side effects (page 17). Applicants maintain that to establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to each claim, that the recited references, when combined, must teach or suggest every limitation of the claim, that one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention, and there would have been a reasonable expectation that the claimed invention would succeed. Applicants also assert

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that the Examiner's combination of cited references is based upon an improper use of hindsight, and that these references are devoid of any motivation to combine their respective teachings (pages 17-18).

On pages 18-23, Applicants argue that the references teach linkers in general, and that Wallach I and Wallach II and Smith teach TNF receptor multimers that are made from monomers held together by any means or by a virtually infinite number of linker permutations, that Paul teaches flexons of 4 to 100 amino acids and does not suggest or mention TNF-receptor based molecules, that the references fail to provide guidance as to how one would arrive at a linker length or an amino acid makeup which would provide the unexpected advantage seen with the instant invention, and at most, and the possibility that one skilled in the art could have optimized a linker length and an amino acid makeup using routine experimentation is merely an invention to experiment further. Applicants also argue that some motivation to select a particular combination in view of a given large group of possibilities must be taught by the prior art.

Applicants' arguments have been fully considered but are not deemed persuasive. Although Wallach I and II and Smith may teach a number of ways of joining TNF receptors to construct multimers, this does not negate the teaching of joining monomers covalently via a peptide linker. Wallach I and II and Smith may not offer experimental results, but they offer ample guidance to one of ordinary skill in the art to determine what an optimal linker length would be, and though some experimentation would be required, such experimentation would be routine. There would be a reasonable expectation of success, since chimeric proteins comprising linker sequences and having desired functional characteristics had been constructed at the time of the invention, and Paul et al. teaches that optimal linker lengths of ten to thirty amino acids

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would allow moieties at either end of the linker to adopt a conformation relatively independently from each other. In response to applicant's argument that there is no suggestion to combine the references and that Paul et al. does not suggest or mention TNF receptor-based molecules, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Wallach I, Wallach II and Smith teach multimers of TNF receptors, and Paul teaches linkers.

Applicants arguments on page 19 of the response that some motivation to select a particular combination in view of a given large group of possibilities must be taught by the prior art, has been fully considered but not deemed persuasive, because even if other possibilities are suggested, there is ample motivation to select *any* of the particular combinations suggested.

Applicants' arguments on pages 20-21 of the invention demonstrates an unexpected advantage, e.g., the increased efficiency in anti-TNF specific activity relative to recombinant Ig-based molecules as evidenced on page 18, lines 3-24 and Table 1 of the instant application, wherein the claimed invention has the same specific activity but at only a third of the concentration required for the Ig-based molecule have been fully considered but are not deemed persuasive. On page 18, lines 13-18, the specification discusses that 57 pg of the dimeric Hu p75 TNF-R ECD in an Ig backbone was needed to inhibit 50% of the killing activity of 63.5 pg of human TNF, as opposed to 20 pg of dimeric Hu TNF-R75 ECD to obtain the same level of

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protection. However, the specification states "This lower than expected activity of the p75 sf2 construct may be due to the partial degradation in this protein (Figure 4) that affected its efficiency." Therefore, it is not apparent that the dimeric Hu TNF-R75 ECD of the instant invention does have an unexpected advantage compared to the dimeric Hu p75 TNF-R ECD in an Ig backbone, since the latter protein was partially degraded, so that the actual concentration needed to inhibit TNF killing was not accurate.

For these reasons and for the reasons cited in the previous office actions, the rejections are maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

- 4.1 Claims 29-31 are allowed.
- 4.2 Claims 1-3, 6, 8, 15-17 and 19-27 are rejected.
- 4.3 Claims 14, 28 and 32-37 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (571) 272-0871.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, se <http://pair-direct.ispto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

A handwritten signature in black ink, reading "Lorraine Spector". The signature is fluid and cursive, with a large loop at the end of the last name.

LORRAINE SPECTOR
PRIMARY EXAMINER